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Aging

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Aging is initiated based on genetic and environmental factors that operate from the time of birth of organisms. Aging induces physiological phenomena such as reduction of cell counts, deterioration of tissue proteins, tissue atrophy, a decrease of the metabolic rate, reduction of body fluids, and calcium metabolism abnormalities, with final progression onto pathological aging. Despite the efforts from many researchers, the progression and the mechanisms of aging are not clearly understood yet. Therefore, the authors would like to introduce several theories which have gained attentions among the published theories up to date; genetic program theory, wear-and-tear theory, telomere theory, endocrine theory, DNA damage hypothesis, error catastrophe theory, the rate of living theory, mitochondrial theory, and free radical theory. Although there have been many studies that have tried to prevent aging and prolong life, here we introduce a couple of theories which have been proven more or less; food, exercise, and diet restriction.

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Aging is an inevitable physiological change occurring in organisms over time. It ultimately 'leads to death naturally as one gets old along with gradual dysfunctions of all organs in the organisms including unicellular organisms, plants, animals, and humans'. Aging is the direct cause of diseases and death in humans so it is one of the biggest questions among many biological phenomena. Despite the efforts from a number of researchers, the progression and the mechanisms of aging are not clearly understood yet.

Along with growth, aging proceeds once humans are born. Based upon aging, many physiological phenomena such as reduction in the number of cellular tissues, a decrease of the metabolic rate, an increase of diseases, and loss of adaptability take place. Such phenomena differ depending on the organs and progress differently as well. The progression of aging is a degenerative change associated with biological characteristics rather than being determined by environmental factors and ultimately indicates that the probability of death is rapidly increasing. The environmental factors that are relevant to lifestyle including stress, exercise, smoking, and exposure to sunlight either accelerate or delay the progression of aging.[1)]

Of various theories with regards to the causes of aging, there are two important theories including genetic programming theories of aging, suggesting that aging and lifespan of organisms are genetically determined, and theories of aging related to primary damage, claiming that aging is induced by the accumulation of damages in organisms from multiple harmful factors. The wear-and-tear theory, error catastrophe theory, the free radical theory, DNA damage hypothesis, loss of adaptive cellular mechanisms, the mitochondrial theory, and the cell membrane theory are known to be included in the theories of aging related to primary damage.[1,2)]

Anatomical and Physiological Changes and Characteristics by Aging

Aging is initiated based on genetic and environmental factors that operate from the time of birth of organisms. Aging induces several physiological phenomena such as reduction of cell counts, deterioration of tissue proteins, tissue atrophy, a decrease of the metabolic rate, reduction of body fluids, and calcium metabolism abnormalities. Such physiological phenomena further lead to several vital impairments such as cardiopulmonary, neurological, endocrine function, immune function, as well as motor function impairments. Therefore, the exposure to risk factors including hypertension, smoking,

hyperlipidemia, glucose metabolism impairment, obesity, food, lifestyle, alcohol, and stress induces multiple diseases in various body systems e.g. dementia, degenerative diseases, stroke, cataract, and hearing loss in the nervous system; hypertension, arteriosclerosis, heart failure, arrhythmias, and pulmonary emphysema in the cardiopulmonary system; stomach ulcer and diverticulum in the digestive system; diabetes in the metabolic system; renal failure in the renal system; osteoporosis and degenerative arthritis in the skeletal system as well as assaults to the human body by tumors, infection, and wounds, with final progression onto pathological aging.[3-9)]

Changes in the central nervous system

Along with aging, the number of cerebral nerve cells is remarkably reduced with an approximately 20% decrease in cerebral blood flow. The size of the brain is then reduced slightly and some neurons are lost in some selected parts of the brain such as the locus ceruleus, substantia nigra, hippocampus, caudate nucleus, putamen, and cerebral cortex. However, there are no sufficient studies showing that the functions of the brain are markedly impaired due to aging. Even though the number of nerve cells is decreased, the rest of the cells compensate for the loss by generating branches. As a result, total dendrites of the cortex and hippocampus are even increased until the forties to sixties. Afterward, the dendrites become reduced in number in the eighties and nineties. Memory, cognitive function, and intellectual functioning become impaired subjectively when people get old but noted abnormalities are not observed in the clinical examinations of elderly people as long as there is an absence of other diseases.

Changes in the neuroendocrine system

It has been well known that the loss of some neurons is accompanied in the neuroendocrine system by aging. If neurons are lost in the hypothalamus, it would have an influence in the broad range, from the pituitary gland to lower target endocrine organs. To the best of our knowledge, however, no studies have reported on the loss of neurons in the hypothalamus induced by aging so far.

Hormones are produced in hypothalamus, pituitary gland, thyroid, parathyroid, pancreas, adrenal, gonads (testicles for men, ovaries for women), and kidney. Of various hormones, female hormones are altered the most by aging. Aging causes not only reduction of sex hormones but also a decrease of production and secretion of renin in the kidney and aldosterone in the adrenals.

The levels of blood cortisol or corticosteroid-binding protein are not much changed in the elderly. This finding is in conflict with the *in vivo* result in rats which suggested that the concentration of cortisol was elevated as the rats aged. However, some hormones are released more as aging is preceded. A greater amount of parathyroid hormone is secreted as people become older and accelerates osteoporosis that occurs in the elderly population due to calcium release in the bones.

Changes in the cardiovascular system

Aging-related changes in the heart generally occur in the myocardial layers. Collagen fibers are rarely observed in the myocardiocytes of normal adults whereas they proliferate with aging and are found mainly around the capillaries of the myocardial layers. Changes in the cardiovascular system are exhibited in arteries particularly and the arterial walls become thick and hard. Glycosylation reaction takes part in hardening the arteries. Because of these anatomical changes, the heart functionally shows decreased diastolic compliance as well as increased pulse pressure. Although cardiac output in the steady state mostly remains unchanged, the maximum heart rate, maximum stroke volume, and circulating blood volume are reduced. Likewise, when the blood entering the arteries is decreased, it inhibits the activity of the baroreceptors so as a result, orthostatic hypotension is commonly found in elderly.

Changes in the skeletal system

The levels of calcium and protein are decreased in bones as people age thereby reducing bone mineral density. Cell degeneration occurs in a wide range of osteoblasts, and irregular bone deposition or resorption takes place due to the exposure of bone surfaces caused by destruction of osteogenic layers to bio-chemical changes. If the cell degeneration becomes worse, it terminates the communication between the cells and introduces lipofuscin in the cells and thereby necrosis occurs. Moreover, the nuclei in osteocytes are hyper-pigmented and become smaller in size. As people become older, the degeneration of cell organelles is more severe so that residual mitochondrial swellings, vacuoles, and aging pigments are observed. Specifically, the cytoplasm swells and cell membranes are destroyed so that the lacunae are filled with the destroyed residuals of osteocytes. The aging-related cartilage degeneration is similar to degeneration in the osteocytes, with the exception that aging pigments do not appear and cell death is more frequently exhibited. Bone mass becomes decreased due to deficiency of the female hormones, reduction of osteocytes, and parathyroid hyperactivity caused by renal dysfunction, and lack of exercise by muscle weakness. The bottom of the radial bones, femoral neck, and spine are easily prone to fracture because of the reduction of bone mineral density by the decrease in bone mass. In addition, the articular cartilages in the joints become deteriorated and worn out, and the carti-

lages lose their elasticity.

Changes in the kidney

The kidney is known to be the organ with the most notable anatomical and physiological changes caused by aging. The size, weight, and volume of the cortex, and the number of glomeruli of kidney are reduced with an increase in age. Also, as congestive degeneration and hardening of glomeruli occur, the glomerular filtration rate (GFR) and the function of renal tubules are lowered. GFR in an eighty year old individual is reduced by 50% of what was observed in their thirties. The reduction of GFR is caused by the decrease of renal cells and hardening of renal vessels and these changes further elevate the risk of renal failure owing to the accumulation of nephrotoxic substances or perioperative ischemic damages. There are not many age-related ureter changes in the urinary system. For the urinary system below the bladder, however, age-related changes occur thereby causing dysuresia, pollakisuria, and urinary incontinence.

Changes in the respiratory system

Based upon the qualitative deterioration in both elastic fibers and collagen fibers, lung tissues become less elastic and expansile. Even if there are no changes in the number of alveoli, the amount of elastic fibers in the alveolar wall is decreased and the size of the alveoli is smaller with slight expansion of the alveolar ducts as well as the respiratory bronchioles. Thus, the elderly are at high risk of atelectasis and postoperative pneumonia owing to gradual reduction of arterial blood PCO_2, an increment of dead space, a decrease of the expiratory volume and expiratory rate, airway cilia impairment, and defense mechanism dysfunctions. Additionally, the respiratory muscles and the thorax are also altered by aging. Weakened respiratory muscles and a stiff diaphragm are exhibited from the age of 55. This seems to be caused by aging-associated scoliokyphosis, calcification of the intercostal cartilages, and spondylarthritis. The reduced diffusion capacity due to aging is induced from a decrease in the lung area owing to damage to the alveoli, an increase in thickness of the alveolar walls, and small-airways obstruction.

The Mechanisms of Aging

Although a number of studies have been carried out regarding the causes of aging so far, it is still not possible to explain them all by a single theory. In other words, research techniques and approaches associated with aging have been varied with the development of life sciences as well as natural sciences, but it is still left to be elucidated what causes aging. Therefore, the authors would like to introduce several theories which have gained attentions among the published theories up to date.

Genetic program theory

According to the genetic program theory, aging is programmed in each species because each species has its own average longevity since they are born. The theory is supported by the fact that the average lifespan in humans has constantly increased in the past 100 years without big changes in the maximum lifespan of humans. The same life curve is shown for animals and plants and in other studies, suggesting that genetic mutations result in prolonged lifespan. This theory posits that aging is the extended genetic signaling of life from the fertilized egg to the grown-up stage. People who support this theory believe the presence of senescence genes control aging-related phenomena due to slowdown or the stoppage of biochemical metabolic pathways. These senescence genes are expressed at different time periods depending on the kinds of cells. During the growth of organisms, a lot of cells are proliferated while many unnecessary cells are disappeared at the same time. Similarly, as the life of unnecessary cells is controlled by the genes based on an accurate timeline, the cells in the aging processes could be managed in the same manner.[10,11]

Wear-and-tear theory

Like machines become damaged and eventually break down when utilized for a certain period of time, the wear-and-tear theory proposes that the human body also undergoes aging due to damage from accidents, diseases, radiation, toxic substances, food, and many other harmful substances when it is utilized for a long time. However, the theory has been rejected because animals protected from the damages also age without any alteration of their maximum lifespan, and therefore, such damages are not the factors causing aging but just time-dependent changes.[1,2]

Telomere theory

The lifespan of a species is strongly associated with the lifespan of the cells that consist of the species. When human fibroblasts are continuously sub-cultured, the lifespan of cell division is estimated to be 50−100 times approximately. Therefore, the lifespan of the cells is considered to be programmed already and it has been reported which shortened telomeres at the chromosomal ends are responsible.

Repetitive DNA sequences, six-nucleotide sequences (TTAGGG), are present at the terminus of all human chromosomes. They are about 12 kbp length and lose telomeres when going through around 100 times of cell division. The length is very similar to the lifespan of cells that are observed while

culturing. Telomerase which prevents against telomere shortening is expressed in immortalized cells and cancer cells with very high activity. Therefore, telomere shortening takes place constantly by the enzyme so that immortalization or proliferation of cancer cells would be ongoing.[12)]

Endocrine theory

The endocrine theory assumes that impaired hypothalamus-pituitary gland-endocrine systems which regulate homeostasis in the body are the main cause of aging and further has many broad effects on many physiological functions in the body. Generally, endocrine hormones participate in controlling growth, metabolism, temperature, inflammation, and stress. This theory is supported by some animal studies, which show that the lifespan of the animals with menopause, andropause, and somatopause (decreased GH/IGH-1) is extended when the corresponding hormones are provided. Since the endocrine system which takes part in the maintenance of life and the species plays significant roles, there are not many changes induced by aging when the hormone system for maintaining the species is greatly altered by aging.[13)]

DNA damage hypothesis

Based on the DNA damage hypothesis, if the DNA with free radical-derived damage is not completely repaired, it would result in reduced gene expression as well as cell death. It would then interfere with the proper functioning of the tissues eventually so that the progression of aging is stimulated. A study, reporting that albino rats, possessing a shorter lifespan than humans, urinate 10 to 15 times more of oxidatively-damaged nucleotides than humans, and the increase in damaged DNA in brains by aging also supports the hypothesis. In addition, it has been known that the ability to repair DNA damages is directly proportional to the lifespan of species and the repair ability is impaired in normal cells due to the progression of aging.[14)]

Error catastrophe theory

The procedures including replication of the DNA, transcription of the gene to produce mRNA, and translation of the message to produce the protein are required in protein synthesis. The theory hypothesizes that if there are any errors in any of those procedures, incorrect genes, mRNA, and proteins would be produced so that the cells would be impaired; however, more studies need to be done in this area in order to support this theory. Even though accumulation of these errors is partially eliminated by the repair system, such a repair system would not operate perfectly and permanently because errors may be accumulated in the repair system as well.[15)]

The rate of living theory

The rate of living theory suggests that energy expenditure is inversely proportional to the lifespan, and in particular, animal studies have shown that the lifespan is shorter when the energy expenditure is higher, and vice versa. In the case of poikilotherms such as nematodes, insects, and fish, their lifespan is generally increased as the habitat temperature is elevated while it is decreased as the temperature is lowered. The lifespan of a housefly at 20℃ is twice that of a housefly at 28℃. Similar to the housefly, the lifespan of a minnow at 10℃ is 1.4 times higher than that of a minnow at 20℃. Another study investigating the relationship between the lifespan of *Drosophila* and temperature showed that approximately 25 days, 50 days, 100 days, and 150 days of lifespan was exhibited at 30℃, 27℃, 21℃, and 18℃, respectively, which is in agreement with this theory. This may be because the metabolic rate would slows down as the temperature is decreased. However, the theory is not applicable for homeotherms as they are mostly independent from the temperature.

The mitochondrial theory

The mitochondrial theory hypothesizes that mitochondria are relevant to aging as mitochondrial DNA where free radicals are produced maximally is not properly protected due to external antioxidants, and mitochondria are very susceptible to damage from external toxic molecules and radioactive materials. Especially, since repair enzymes for the damaged DNA do not exist in mitochondria, that damage has significant implications. The damaged mitochondrial DNA leads to a decrease of energy production, an increase of free radical production, and accumulation of harmful molecules. Several aging phenotypes are exhibited when mitochondrial DNA is studied in animal studies done with mice. When mitochondrial DNA polymerase deletion exists, it is known that the aging process is expedited thereby shortening the lifespan. Aging induces alterations in mitochondrial morphology as well as functional impairments. It further reduces ATP generation and therefore elevates oxidative stress.[16,17)]

Free radical theory

Oxidative damage is introduced to organisms by several free radicals [superoxide (O^{2-}) and hydroxyl (OH^{-}) anions, nitric oxide (NO), peroxynitrite ($ONOO^{-}$)] which may be produced incidentally in the normal metabolic processes. The free radical theory suggests that the accumulation of these types of damage finally results in aging. Other results from animal studies, showing that the oxidatively damaged products of tissues by free radicals such as lipofuscin, lipid hydroperoxides, malondialdehyde, carbonyl group, and 8-hydroxy-2-

deoxyguanosine were exhibited more when the animals were older, also support the theory indirectly. If the free radical theory is correct, the lifespan should be prolonged by preventing free radical-induced oxidative damage when administering antioxidants in experimental animals. However, even though many researchers have attempted to prove the hypothesis, no positive results have been shown yet.

Organisms possess various defense systems in order to protect themselves from the toxicity of free radicals. As the primary defense system for prevention of damage, there are antioxidant compounds including vitamin E, β-carotene, ascorbic acid, and uric acid as well as antioxidant enzymes including superoxide dismutase, glutathione peroxidase, glutathione reductase, DT-diaphorase, and catalase.

Lipolytic enzymes (phospholipase A2), proteolytic systems (proteinases and peptidases), and DNA and RNA repair systems (endonuclases and exonucleases) are included in the secondary defense system to remove or repair the damaged products.[18,19]

Studies Regarding the Prevention of Aging

Although there have been many studies that have tried to prevent ageing and prolong life, here we introduce a couple of theories which have been proven more or less.

Food

Although various kinds of food are recommended, no innovative food has yet been found. However, general healthy foods such as berries and leafy greens, protein, omega-3-rich fish, whole grains, and red wine have been introduced as anti-aging foods.

It is known that berries and leafy greens include disease-fighting antioxidants, vitamin B, C, E, K, anti-inflammatory compounds, and a variety of phytonutrients including beta-carotene, lutein, and zeaxanthin. Protein is also identified as an important component of every cell in the body and quick weight loss. In the case of whole grains, they contain dietary fiber, protein, essential fatty acids, and vitamins so that they help to lower cholesterols along with the antioxidants. In addition to whole grains, red wine possesses flavonoids, catechins, saponins, and guercetin. When one or two cups of red wine are consumed by females and males in their middle age, respectively, it has been known that the risk of heart attack is lowered by 30−50% approximately.

Exercise

Since an insufficient amount of exercise can cause many adverse effects in our body, it cannot be emphasized enough how important exercise is. A shortage of exercise results in muscle and skeletal weight loss, cardiovascular dysfunction, lethargy, and stiff joints regardless of age. For the elderly, especially the handicapped elderly, exercise should be performed in accordance with their physical capacity due to decreased endurance. Excessive exercise could lead to several complications such as musculoskeletal impairments, fever, severe fatigue, as well as myocardial infarction and even sudden death.[20,21]

Diet restriction; calorie reduction without malnutrition

Even though human studies have not been performed due to ethical and time issues, animal studies have proved that a calorie-restricted diet can extend lifespan. The average lifespan and maximum lifespan with ad libitum was 7 days and 13 days for protozoa, 30 days and 42 days for water flea, 50 days and 100 days for spiders, 33 months and 54 months for guppy, 23 months and 33 months for white rats, and 75 years and 110 years for humans, respectively. Compared to the ad libitum, on the other hand, increased average lifespan and maximum lifespan were exhibited in all the species with caloric restriction which were 13 days and 25 days for protozoa, 51 days and 60 days for water flea, 90 days and 139 days for spiders, 46 months and 59 months for guppy, 33 months and 47 months for white rats, respectively.

A study with the Fischer 344 Rat found that the average lifespan as well as the maximum lifespan were extended as the length of diet restriction was increased; the average lifespan and maximum lifespan were 701 days and 941 days with ad libitum, 1046 days and 1296 days with caloric restriction after 6 weeks, 808 days and 1040 days with caloric restriction from 6 weeks to 6 months only, 941 days and 1299 days with caloric restriction after 6 months, and 810 days and 969 days with ad libitum but protein restricted.[22,23]

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